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Hypophosphatemia

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Hypophosphatemia is a common laboratory abnormality that occurs in a wide variety of disorders. When severe and prolonged, it may be associated with rhabdomyolysis, brain dysfunction, myocardial failure and certain defects of erythrocyte function and structure. Other disorders ascribed to hypophosphatemia, including platelet dysfunction and thrombocytopenia, liver dysfunction, renal tubular defects, peripheral neuropathy, metabolic acidosis and leukocyte dysfunction are less well documented. In quantitative terms, the most severe phosphate deficiency is seen in patients who consume a phosphate-deficient diet in conjunction with large amounts of phosphate-binding antacids, in persons with severe, chronic alcoholism and in patients with wasting illnesses who are refed with substances containing an inadequate amount of phosphate. When severe hypophosphatemia occurs in such a setting, the clinical effects appear to be much more pronounced. While there have been some advances in our understanding of the pathophysiology of phosphate depletion and hypophosphatemia, much remains to be learned. Treatment of hypophosphatemia is controversial; however, there is little question that it is indicated in alcoholic patients and those with severe phosphate deficiency.

MODERATE HYPOPHOSPHATEMIA, arbitrarily defined as a serum phosphorus level ranging between 1.0 and 2.5 mg per dl, occurs under numerous circumstances (Table 1). Being a highly reactive ion involved in many chemical reactions, phosphate is readily taken up from extracellular fluid into cells and incorporated into several organic compounds. Persistent moderate hypophosphatemia is an important finding because it may reflect such disorders as vitamin D deficiency, hyperparathyroidism or a reabsorptive defect of the renal tubule. In most instances, hypophosphatemia of itself is no more than an interesting evanescent biochemical bystander. Little difficulty appears to result from moderate hypophosphatemia per se. When concentrations fall below 1.0 mg per dl and remain at that level for two or more days, however, serious consequences may occur.

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Causes of Severe Hypophosphatemia

The conditions associated with severe hypophosphatemia, herein defined as a serum phosphorus level of less than 1 mg per dl, are shown in Table 2. The most common cause of this condition is chronic alcoholism and alcohol withdrawal. Hypophosphatemia is especially common in alcoholic patients in hospital.[1-3] In such patients, serum phosphorus levels may be normal initially but decline to extremely low values after

ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
AMP = adenosine monophosphate
ATP = adenosine triphosphate
CNS = central nervous system
2,3-DPG = 2.3-diphosphoglycerate
LD_{50} = lethal dose, median
P_{50} = partial pressure of oxygen at which hemoglobin is 50 percent saturated

one to three days. With the onset of hypophosphatemia, phosphate in the urine virtually disappears. This presumably indicates cellular uptake of inorganic phosphate as administered nutrients are metabolized. Such severe hypophosphatemia could also be the result of acute respiratory alkalosis. In nearly all cases of severe alcoholism, respiratory alkalosis occurs during withdrawal.[3,4]

Measurement of skeletal muscle composition in patients with severe alcoholism shows that phosphate deficiency almost always exists.[4] The cause of phosphate deficiency in these patients is not completely understood. While one could certainly implicate deficient intake, malnutrition cannot always be shown. Studies in our laboratory on dogs given intoxicating doses of alcohol twice a day for only four weeks showed a substantial reduction of total muscle phosphate despite a nutritious diet and an abundant intake of this mineral.[5]

Ingestion of phosphate-binding antacids such as aluminum hydroxide or aluminum carbonate may cause phosphate depletion and hypophosphatemia. In human volunteers fed a low phosphate diet and large quantities of phosphate-binding antacids, severe hypophosphatemia and phosphate deficiency developed.[6] In most clinical circumstances, ingestion of antacids does not cause phosphate deficiency unless dietary intake of the mineral is severely restricted.

Severe hypophosphatemia has been noted in patients suffering widespread, severe thermal injury. It usually appears during the first few days after the burn.[7] In such patients, phosphate excretion is substantially depressed and respiratory alkalosis is the rule. Some evidence exists suggesting that the incidence of burn wound sepsis may be increased as a result of hypophosphatemia.

Uncontrolled diabetes mellitus with heavy glycosuria is a well-established cause of phosphate depletion. Phosphate is excreted excessively into the urine as a result of osmotic diuresis. In addition, metabolic acidosis depresses phosphorylation, tends to elevate serum phosphorus concentration and thereby intensifies phosphaturia. Thus, severe phosphate deficiency may occur in diabetic ketoacidosis.[1] Administration of insulin and fluids results in a rapid decline of serum phosphorus levels and disappearance of phosphate from the urine. Severe hypophosphatemia is common during recovery from diabetic ketoacidosis.

TABLE 1.—*Causes of Moderate Hypophosphatemia*

Hemodialysis	Volume expansion
Hyperparathyroidism	—Aldosteronism (licorice)
Starvation	—Saline infusion
Glucose administration	—Hypokalemia
Fructose administration	Hypomagnesemia
Glycerol administration	Gram-negative bacteremia
Lactate administration	Insulin administration
Sodium bicarbonate infusion	Gastrin administration
Osteomalacia	Glucagon administration
Renal tubular defects	Epinephrine administration
Pregnancy	Corticosteroid administration
Malabsorption	Diuretic therapy
Vitamin D deficiency	Androgen therapy
Acute gout	Recovery from hypothermia
Salicylate poisoning	

TABLE 2.—*Causes of Severe Hypophosphatemia*

Chronic alcoholism and alcoholic withdrawal
Pharmacologic phosphate binding
Severe thermal burns
Recovery from diabetic ketoacidosis
Hyperalimentation
Nutritional recovery syndrome
Respiratory alkalosis
Postrenal transplantation

Administration of calories and other nutrients in excess of requirements to patients who have lost weight may result in severe hypophosphatemia. Their shrunken cells must be capable of an anabolic response. Hypophosphatemia occurs as a result of synthesizing protoplasm with inadequate quantities of phosphate.

The nutritional recovery syndrome represents a constellation of findings observed during the refeeding of patients with severe protein-calorie malnutrition or starvation. In contrast to hyperalimentation, hypophosphatemia may occur during administration of calories *in normally required quantities*. Most observations of this syndrome were made while treating prisoners of war at the end of World War II. Refeeding, especially when simple carbohydrates were given overzealously, was sometimes followed by peripheral edema, ascites and hydrothorax. Sudden death was common. Administration of brewer's yeast did not consistently prevent these complications.[8] However, refeeding with skim milk was apparently

associated with less morbidity. Unfortunately, obtaining measurements of chemical composition of the blood or urine from those patients was not possible. This syndrome can be reproduced in experimental animals and is commonly seen during overzealous feeding of patients who have lost large quantities of weight as result of food faddism or anorexia nervosa. Based on clinical descriptions, such patients closely resemble the prisoners after World War II. In addition to hypophosphatemia provoked by nutrients, most of these patients show other serious disturbances such as hypokalemia, hypomagnesemia and severe glucose intolerance. The observation that feeding with small quantities of skim milk rather than pure carbohydrates caused less morbidity may very likely be ascribed to the phosphate and potassium content of skim milk.

Severe respiratory alkalosis can cause severe hypophosphatemia. Studies of normal subjects have shown that serum phosphorus concentrations may fall below 0.5 mg per dl after voluntary hyperventilation.[9,10] Respiratory alkalosis is probably one of the most common causes of severe hypophosphatemia in patients in hospital. Hyperventilation may apparently accompany metabolic encephalopathy resulting from alcoholic withdrawal, or simply may be the result of fear and pain. Respiratory alkalosis can be especially prominent in patients with sepsis and bacteremia. The mechanism of hypophosphatemia under such conditions is clear. Reduction of carbon dioxide in the blood is associated with an equally rapid reduction of carbon dioxide in the cells. The associated elevation of intracellular pH activates phosphofructokinase which in turn accelerates phosphorylation of glucose[11]; phosphate ions are rapidly taken up from serum and hypophosphatemia results. Simultaneously, phosphate virtually disappears from the urine. On the other hand, if an equal degree of alkalosis is induced by infusing sodium bicarbonate, serum phosphorus concentration falls only slightly and excretion of phosphate in the urine *increases*.[10] The increase of phosphate excretion occurs by two mechanisms. First, a slight expansion of extracellular fluid volume occurs as a result of bicarbonate infusion and this reduces reabsorption of phosphate in the proximal tubule. Second, because of plasma volume expansion and a slight reduction of serum calcium concentration, parathyroid hormone levels increase during bicarbonate infusion and serve to decrease tubular reabsorption of phosphate.

TABLE 3.—*Consequences of Severe Hypophosphatemia*

Rhabdomyolysis
Erythrocyte dysfunction and hemolysis
Myocardial dysfunction
Leukocyte dysfunction
Platelet dysfunction
Central nervous system dysfunction
Metabolic acidosis
Osteomalacia

Severe hypophosphatemia has also been noted in some patients who have had renal transplants. Such patients apparently have a renal tubular reabsorptive defect that permits excessive loss of phosphate into the urine. This has often occurred during corticosteroid therapy and administration of phosphate-binding antacids, both of which could conceivably favor development of hypophosphatemia.

Consequences of Acute Hypophosphatemia

Current evidence suggests that there are at least eight definite harmful consequences of severe hypophosphatemia. These are illustrated in Table 3. That other tissues, organs or physiological functions are affected appears likely.

Rhabdomyolysis

Rhabdomyolysis, or acute necrosis of skeletal muscle, is one of the most common and reproducible consequences of phosphate deficiency and severe hypophosphatemia. In most cases it is recognized by the appearance of abnormal elevations of muscle enzymes in serum, such as creatine phosphokinase or aldolase. When severe, it may be associated with overt physical findings of muscle necrosis, including profound weakness, pain, stiffness, tenderness and edema of involved muscles and, sometimes, the appearance of myoglobin in the urine. In most cases of hypophosphatemia, rhabdomyolysis is clinically mild or asymptomatic and reflected only by elevated levels of muscle enzymes. This occurs most commonly in persons with chronic alcoholism; however, it has also been seen in patients who become hypophosphatemic as a result of hyperalimentation for weight loss. It is rarely observed during recovery from diabetic ketoacidosis. Measurement of muscle composition in such patients has invariably shown severe deficiency of phosphate. At least in patients with chronic alcoholism, phosphate deficiency occurs in association with other disturbances, including mag-

nesium deficiency and, in some but certainly not all cases, a moderately low content of potassium. Tissue content of sodium, chloride, water and calcium is nearly always substantially elevated in such patients.[4] To my knowledge, there have been no reports of rhabdomyolysis with severe hypophosphatemia as a result of respiratory alkalosis if body stores of phosphate are normal. Experimental studies on dogs support this observation. On the other hand, a reversible electrochemical defect of skeletal muscle cells appears after feeding a diet containing all essential nutrients except phosphate. This defect is reversible on repletion with phosphate. However, if an animal with preexisting phosphate deficiency is subjected to hyperalimentation without phosphate, hypophosphatemia is promptly induced, and severe rhabdomyolysis supervenes.[12,13] Dogs fed intoxicating doses of ethanol each day will eventually show depletion of skeletal muscle phosphate despite an adequate phosphate intake.[14]

Erythrocytes in Hypophosphatemia

The most important biochemical abnormalities of erythrocytes associated with phosphate deficiency and severe hypophosphatemia include a decline of 2,3-diphosphoglycerate (2,3-DPG) and a decline of adenosine triphosphate (ATP).[15] Inorganic phosphate in erythrocytes is in diffusion equilibrium with plasma phosphate. Consequently, both 2,3-DPG and ATP may become reduced in the presence of severe hypophosphatemia.

An important interaction occurs between hemoglobin and 2,3-DPG that promotes release of oxygen.[16] This has been quantitated by means of the index, P_{50}, which is a value for oxygen tension of mixed venous blood at 37°C, pH 7.4, at which hemoglobin is 50 percent saturated. Low levels of 2,3-DPG may depress P_{50} values or shift the oxyhemoglobin saturation curve to the left so that release of oxygen to peripheral tissues is diminished. Thus, acute hypophosphatemia, when associated with a serious decline of 2,3-DPG may limit release of oxygen at the cellular level and thereby create anoxia. The interaction of hemoglobin with 2,3-DPG occurs at the same molecular site of hemoglobin glycosylation in patients with persistent hyperglycemia. It is possible, therefore, that a potentiation of impaired oxygen delivery could occur in phosphate deficient, hypophosphatemic and persistently hyperglycemic patients with diabetes mellitus. An additional potentiating factor in patients with diabetes could be the presence of metabolic acidosis. This would favor decomposition of 2,3-DPG, independent of hyperglycemia or phosphate deficiency.

Structural defects of erythrocytes in phosphate deficiency and hypophosphatemia include increased rigidity and in rare instances hemolytic anemia.[17,18] Hemolysis has also been described in patients with chronic uremic acidosis in whom serum phosphorus has been profoundly depressed by excessive ingestion of phosphate-binding antacids.[15,18,19] Hemolysis is actually a rare complication of severe hypophosphatemia. When it has occurred, ATP content has invariably been less than 15 percent of normal. Hemolysis is usually provoked by an unusual stress on the metabolic requirements of erythrocytes such as severe metabolic acidosis.

Myocardial Dysfunction

If phosphate deficiency and hypophosphatemia were sufficiently severe to reduce the content of 2,3-DPG in erythrocytes, one might predict that release of oxygen to tissues would diminish as a result of shifting the oxyhemoglobin dissociation curve to the left and, in response, the resting cardiac output would necessarily rise. One might further speculate that if a high resting cardiac output occurred by this means, such a condition, especially in a case of severe alcoholism, might lead one to suspect underlying vitamin deficiency and beriberi heart disease. However, data are not available to verify such speculations.

Fuller has examined the effects of pure phosphate deficiency on myocardial performance in dogs.[12,20] These animals were gavage-fed a diet that was normal in all respects except that it contained only trace quantities of phosphate. Transducers were implanted surgically for measurement of ascending aortic root blood velocity and left ventricular pressure. The dogs were studied while awake. Their serum phosphorus values had fallen from 5.1 to 0.9 mg per dl and muscle phosphate concentration had fallen from 28 to 22.6 mmoles per 100 grams fat free dry weight. When phosphate deficiency existed, stroke volume, peak blood flow velocity, maximum ascending aortic blood flow acceleration and maximum left ventricular rate of change of pressure (dp/dt) had decreased significantly. Restoration of phosphate to the diet corrected all of these abnormalities. Although the relationship between 2,3-DPG in

erythrocytes and oxyhemoglobin dissociation may not be the same in dogs as in humans, it was clear that experimental phosphate deficiency and hypophosphatemia resulted in a hypodynamic effect on the heart rather than the speculated high-output state.

Somewhat similar observations have been made by O'Connor and his co-workers[21] regarding critically ill patients whose average serum phosphorus concentration was 0.97 mg per dl (range 0.7 to 1.4 mg per dl). After infusing 1,000 mg of phosphorus (as phosphate) in 60 ml of fluid volume, cardiac output did not change significantly but calculated stroke work rose. The latter occurred independently of Starling effects and probably represented an improvement in myocardial contractility.

Perhaps the most important clinical observations to date on hypophosphatemic cardiomyopathy were made by Darsee and Nutter.[22] They studied the cases of three patients with severe congestive cardiomyopathy and florid heart failure. In the first patient, who was alcoholic, the serum phosphorus level was 0.4 mg per dl. In the second, a 42-year-old man who had ingested large quantities of aluminum hydroxide gel for several months, the serum phosphorus level was 0.6 mg per dl. In the third patient the serum phosphorus level was 0.3 mg per dl, and aluminum hydroxide gel also had been consumed. All three patients recovered completely from their congestive cardiomyopathy following restoration of serum phosphorus levels to normal. Of importance, only the first patient received digitalis and diuretics, the second and third patients did not. These observations suggest that correction of hypophosphatemia itself reversed cardiomyopathy.

Although severe hypophosphatemia occurs commonly in a wide variety of circumstances, recognition of congestive cardiomyopathy or overtly impaired ventricular function in hypophosphatemia is highly unusual. The reason for this may be explained by preliminary experimental studies from two different laboratories. In our laboratory we have examined the effects of hyperalimentation-induced hyposphatemia on dogs whose weight had been reduced by caloric restriction. Despite an appreciable fall of skeletal muscle phosphate content during hyperalimentation, myocardial content of inorganic phosphate, ATP, adenosine diphosphate (ADP) and total phosphorus remained within normal limits. These findings existed in the face of serum phosphorus concentrations of less than 1 mg per dl. These findings suggest that the heart, being vital to life, has protective mechanisms that maintain vital energy substrates at the expense of skeletal muscle.

Darsee has also examined this problem in rats maintained on a phosphate-free diet and phosphate-binding antacids for seven weeks.[23] Although levels of serum and skeletal muscle phosphorus were depressed significantly, cardiac muscle phosphate levels were normal. Preliminary studies in their laboratories suggested that the clinical appearance of hypophosphatemic cardiomyopathy was usually preceded by an event that caused sudden release of residual myocardial phosphate into the blood stream. In experiments using dogs, they showed that following ten minutes occlusion of the midportion of the left anterior descending coronary artery, myocardial contractility was substantially decreased in phosphate-depleted dogs but not in normal dogs with the same duration of coronary occlusion. Such findings might mean that although total phosphate, inorganic phosphate and perhaps even the adenylic acid pool remain normal in hearts of phosphate-deficient dogs, the metabolic state and potential contractility of the myocardium are extremely tenuous and fail with insults that would not ordinarily affect muscle performance.

Increased attention should be paid to the effects of phosphate deficiency on the heart. Although frank congestive cardiomyopathy under such conditions appears to be rare, it nevertheless appears to be one of the few types of congestive cardiomyopathy that is curable.

Leukocyte Function During Hypophosphatemia

A serious complication of intravenous hyperalimentation therapy is systemic infection by bacterial and fungal organisms. Hypophosphatemic dogs show severe depression of chemotactic, phagocytic and bactericidal activity of granulocytes. These abnormalities are reversed on correction of hypophosphatemia.[24] Similar observations have been made on a patient who became hypophosphatemic during hyperalimentation.[18]

Respiratory alkalosis and hypophosphatemia may occur in association with Gram-negative bacteremia.[25] Guinea pigs infected with *Salmonella* organisms became hypophosphatemic before death. When given phosphate, however, mortality was substantially reduced and fewer organisms were found in their tissues.[26]

Apparently, hypophosphatemia impairs granu-

locyltic function by disrupting ATP synthesis. ATP provides energy for contractions of microfilaments, which in turn regulate the mechanical properties of leukocytes—namely, pseudopod and vacuole formation.[27]

Platelet Function During Hypophosphatemia

Seven abnormalities of platelet function and structure have been observed in hypophosphatemic dogs: (1) thrombocytopenia, (2) increased platelet diameter suggesting shortened platelet survival, (3) megakaryocytosis of the marrow, (4) a fivefold to tenfold acceleration in rate of disappearance of labeled platelets from blood, (5) impairment of clot retraction, (6) a 44 percent reduction in platelet ATP content and (7) hemorrhaging into the gut and skin. These abnormalities can be circumvented if phosphate supplements are provided.[28] Similar changes have not been observed in humans.

Effects of Hypophosphatemia on the Central Nervous System

Some patients with severe hypophosphatemia have symptoms compatible with a metabolic encephalopathy.[18,29] In sequence, irritability, apprehension, weakness, numbness, paresthesias, dysarthria, confusion, obtundation, convulsive seizures and coma occur. This clinical syndrome has been observed in patients without other apparent causes for encephalopathy who have received intravenous hyperalimentation therapy as well as in patients during withdrawal from chronic alcoholism. In contrast to delirium tremens, hallucinations have not been observed. Obviously, both conditions may coexist.

The relationship between hypophosphatemia and the decline of erythrocyte 2,3-DPG becomes especially important in tissues where oxygen is necessary for energy production. This could have an important role in the brain where oxidation of glucose through the Krebs cycle is necessary for synthesis of ATP.

In one report,[18] it was found that in three of the eight patients who became hypophosphatemic during hyperalimentation, paresthesias, mental obtundation and hyperventilation developed. In those whose P_{50} values were abnormally low there was diffuse slowing in the frequency of electrical impulses on their electroencephalograms. These changes disappeared when hypophosphatemia was corrected. Perhaps the best evidence that hypophosphatemia plays a role in this encephalopathy has been the observation that it does not occur in patients receiving hyperalimentation with adequate phosphate.

Metabolic Acidosis

Substantial clinical and experimental evidence is now available indicating that severe metabolic acidosis may occur in the presence of phosphate deficiency and severe hypophosphatemia. When phosphate is removed from the diet or its absorption is prevented by binding with antacids, bone minerals are promptly mobilized. This apparently occurs even before the advent of hypophosphatemia and suggests operation of an unidentified hormone. Phosphate deficiency in a child, or in an adult who has a disease process causing rapid turnover of bone, may cause hypercalcemia. Independently of hypercalcemia, phosphate deficiency nearly always causes hypercalciuria. Phosphate deficiency thus induced is seldom associated with metabolic acidosis. However, as hypophosphatemia becomes more severe, phosphate ions virtually disappear from the urine thereby eliminating the capacity to excrete metabolic hydrogen as titratable acid. The bulk of metabolic acid is excreted by exchange of hydrogen ions ($H+$) from the cell with sodium ions ($Na+$) from the renal tubular lumen. In this process, Na_2HPO_4 is converted to NaH_2PO_4 and the hydrogen ions are measurable as titratable acid. If phosphate is absent from the urine, metabolic acid can be excreted by the reaction $NH_3+H^+ \rightleftharpoons NH_4^+$. Ordinarily, a decline of intracellular pH would augment production of ammonia (NH_3). However, in phosphate deficiency, it has been proposed that intracellular pH rises, thereby decreasing NH_3 production. A rise of intracellular pH in phosphate deficiency has been shown to occur in liver and muscle.[30] Whether similar changes occur in the kidney cell has not been determined. Nevertheless, abundant evidence shows that phosphate deficiency reduces ammonia excretion and thus supports the theory that the intracellular pH of renal cells rises. Thus, the decrease in ammonia production and unavailability of buffer phosphate in the urine essentially prevent excretion of metabolic acids.

The question arises as to why profound metabolic acidosis does not regularly develop in persons who cannot excrete titratable acid or form ammonium. The explanation lies in the fact that during mobilization of bone mineral, there also occurs mobilization of carbonate, which is an im-

portant component of bone apatite (Figure 1). Sufficient carbonate is mobilized from bone to titrate metabolic acid. In fact, in studies using animals it has been found that carbonate mobilization may overshoot and result in slight metabolic alkalosis. However, should some event occur that prevents mobilization of bone mineral, metabolic acidosis of severe proportion can occur. This has been described in children with severe lactase deficiency and protein-calorie malnutrition during refeeding without adequate phosphate. Addition of phosphate to their dietary mixture resulted in pronounced increments of acid excretion into the urine and correction of metabolic acidosis. Experimentally, bone mobilization resulting from phosphate deficiency also prevents metabolic acidosis. However, metabolic acidosis rapidly supervenes if agents are administered that interrupt mobilization of bone mineral such as diphosphonate or colchicine.[31] Although it might be possible that the mild state of hyperchloremic metabolic acidosis that regularly occurs during recovery from diabetic ketoacidosis is a result of phosphate deficiency and hypophosphatemia, there is no evidence to support this notion.[32]

Besides the metabolic interplay of bone mineral mobilization and altered excretion of acid by the kidney, there also may occur a depression of bicarbonate reabsorption in the proximal tubule.[30,33] However, Schmidt[34] was unable to reproduce these findings. The potential clinical importance of proximal tubular bicarbonate wasting in phosphate depletion has not been established.

Osteomalacia

Mobilization of bone mineral during phosphate deficiency and hypophosphatemia, when present for a sufficiently long time, may result in clinically evident osteomalacia. Such a condition has been described by Cooke and her associates.[35] Their patient had ingested a diet deficient in phosphate and had consumed large quantities of phosphate-binding antacids for a prolonged time. In the classic studies conducted by Lotz and Barrter,[6] dietary deprivation of phosphate and ingestion of phosphate-binding antacids was associated with hypercalciuria. When serum phosphorus levels approached 1 mg per dl or less, the patients complained of weakness and bone pain and were thought to have all of the clinical features of osteomalacia. However, their symptoms were relieved promptly on restoration of phosphate to their diets and elimination of phosphate-binding

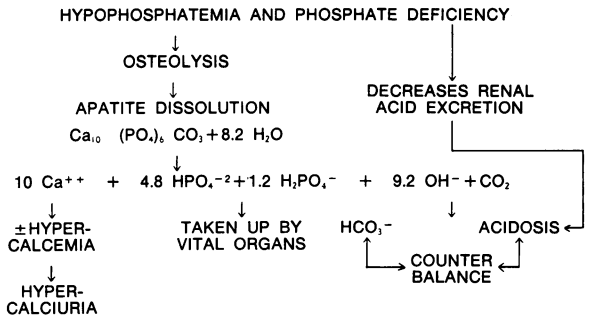


Figure 1.—Deprivation of phosphate stimulates dissolution of the skeleton in an apparent attempt to maintain a normal serum phosphorus concentration. Apatite breaks down to calcium, phosphate, carbonate and water. Hypercalcemia occurs in children or in any person if increased bone turnover prevails. Hypercalciuria is a regular feature. Although urine phosphate is sufficiently depressed to prevent acid excretion as titratable acidity, carbonate ions mobilized from apatite titrate the retained metabolic acids sufficiently to prevent metabolic acidosis. If this process is long-standing, classic osteomalacia may result.

antacids. Hypercalciuria appears to be an aspect of phosphate deficiency found more often in women than in men.[36]

Unproved Consequences of Hypophosphatemia

Because adequate supplies of inorganic phosphate are critical for repletion of ATP stores in every cell, it seems conceivable that any tissue or organ may become damaged in the presence of severe hypophosphatemia. Descriptions of muscular paralysis independent of rhabdomyolysis have appeared.[37,38] Unfortunately, the patients in one report[38] were also acutely hypokalemic. Thus, the role of hypophosphatemia was unclear. That hepatocellular dysfunction might occur in severe hypophosphatemia was first suggested by Frank and Kern in 1962.[39] They described a 51-year-old woman with alcoholic cirrhosis whose serum phosphorus level had fallen to 0.5 mg per dl in the wake of respiratory alkalosis. Her bilirubin level rose appreciably and she became comatose. During the following few days her serum phosphorus levels returned to normal and abnormal neurological findings cleared. We have also observed this sequence of events in alcoholic patients in hospital and, therefore, question the possibility that spontaneous correction of hypophosphatemia by release of phosphate from injured skeletal muscle may be inadvertently life-saving in such patients.

Severe hypophosphatemia may alter the redox (reduction-oxidation) state of cytosol and con-

ceivably be responsible for lactic acidosis or β-hydroxybutyric ketoacidosis.[40] Unfortunately, studies have not been conducted to determine if pancreatitis or even intestinal function could be impaired by hypophosphatemia.

Mechanism of Cellular Injury in Hypophosphatemia

In hypophosphatemia and phosphate deficiency, critical determinants of cellular injury appear to be the prevailing concentration of inorganic phosphate and adenine nucleotides in the cytosol. In particular, if the concentration of cytosolic ATP falls to a critically low level, cellular dysfunction or disintegration may follow. The supply of inorganic phosphate in the cytosol is critical for resynthesis of ATP from ADP.[41]

Unquestionably, combined phosphate deficiency and severe hypophosphatemia can result in widespread cellular damage. On the other hand, whether hypophosphatemia independent of phosphate deficiency can induce cellular damage or dysfunction is unclear. One study, published in abstract form only, showed that experimental animals given *Salmonella* organisms intravenously became hypophosphatemic as the result of respiratory alkalosis.[26] When sufficient phosphate to prevent hypophosphatemia was given along with the same dose of bacteria, the LD_{50} (lethal dose, median) was significantly increased. Similarly, prevention of severe hypophosphatemia may reduce the incidence and morbidity from burn wound sepsis and bacteremia in patients with severe thermal burns (D. Haburchak, US Army, Institute for Surgical Research, Fort Sam Houston, TX, oral communication, June 1978).

Energy requirements to maintain cellular function and integrity may undergo rapid fluctuation, and these variable demands must be integrated and transmitted to mitochondria where energy is produced. At any given instant, the mitochondrial respiratory rate must respond to these minute-to-minute changes in cellular demands. This cellular energy state is reflected by several substrate concentration ratios.[42] For example, the lactate to pyruvate ratio indicates the cytosolic redox state, while that of mitochondria is reflected by the ratio of β-hydroxybutyrate to acetoacetate. However, the overall energy state of the cell is perhaps best represented by the phosphorylation potential.[43] This is defined as the ratio of cytosolic ATP to the product of cytosolic ADP and inorganic phosphate:

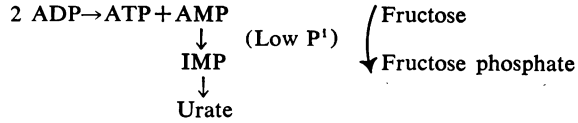
$$\text{Phosphorylation potential} = \frac{[\text{ATP}]}{[\text{ADP}] \times [\text{P}^{\text{i}}]}$$

Any metabolic alteration that increases the value of the phosphorylation potential slows mitochondrial respiration. In contrast, if the phosphorylation potential decreases, mitochondrial respiration accelerates. Thus, a reduction of cytosolic inorganic phosphate increases the potential and slows mitochondrial respiration. By this mechanism, ATP levels fall and reduce the ATP to ADP ratio, thereby normalizing the phosphorylation potential.

Besides affecting the mitochondrial respiratory rate,[44] intracellular inorganic phosphate concentration is also an important regulator of the overall adenine nucleotide pool size. ADP, AMP (adenosine monophosphate) and ATP are in equilibrium through the myokinase reaction:

$$2\ \text{ADP} \rightleftharpoons \text{AMP} + \text{ATP}$$

A major degradation pathway for the adenylate pool is the irreversible deamination of AMP to inosine monophosphate (IMP) catalyzed by the enzyme AMP-deaminase. This reaction is strongly inhibited by a normal concentration of intracellular phosphate. Thus, a pronounced reduction in intracellular phosphate deinhibits AMP-deaminase, resulting in AMP degradation and is in turn reflected throughout the adenylate pool. This phenomenon is exemplified by the response to intravenously given fructose.[45] Fructose is metabolized by three tissues: intestinal mucosa, liver and renal cortex. Its phosphorylation by these tissues is facilitated by fructokinase. Formation of fructose phosphate is unregulated, meaning that increasing concentrations of fructose phosphate in the cytosol do not inhibit further uptake of fructose. Thereby, the cytosolic concentration of inorganic phosphate is sharply lowered, AMP-deaminase is deinhibited and the adenylate pool is reduced. In patients with hereditary fructose intolerance, the product of AMP deamination, inosine, and its product, uric acid, appear in the urine in increased quantities following administration of fructose.[46] This reaction is illustrated as follows:



This sequence of events occurs very rapidly and has been associated with functional and structural disturbances in the liver and kidney.[47] Adminis-

tration of inorganic phosphate provides partial protection against these harmful effects.

A sustained, severe reduction of inorganic phosphate concentration in the cells will reduce the cytosolic concentration of ATP. This can potentially result in a critical deficiency of ATP for energy-requiring reactions. The fall of ATP concentration activates 5′ nucleotidase which has an additional "self-destructive" effect by further reducing the adenylic acid pool.

Although information is not complete, certain tissues appear to be more susceptible to hypophosphatemia than others. For example, intracellular concentration of inorganic phosphate in erythrocytes is dependent on diffusion down a chemical gradient from plasma (in other words, in order for phosphate to enter the erythrocyte, the phosphate concentration in plasma must exceed that in cytoplasm). Thus, hypophosphatemia leads to a reduction of cellular inorganic phosphate, and this in turn reduces the cell's capacity to produce ATP. This process, apparently, would be independent of the reduced 2,3-DPG, which in turn would alter the cell's capacity to release oxygen. If an additional metabolic stress is superimposed, such as severe acidosis, hemolysis may occur.[27] Hemolysis has been observed only when ATP concentrations have fallen to very low values. In contrast to the erythrocytes, other tissues apparently have the capacity to maintain more adequate supplies of intracellular inorganic phosphate despite hypophosphatemia. In our own studies,[48] dogs were fed a calorie-restricted diet containing abundant phosphate. When their baseline body weight had been reduced by a third, hyperalimentation was carried out without adequate phosphate until their serum phosphorus levels fell to 1.0 mg per dl or less. Although total muscle phosphate fell rapidly during hyperalimentation, muscle inorganic phosphate concentration remained normal as also did the concentrations of ATP and ADP. Thus, both the phosphorylation potential and the adenylate pool remained normal. These observations suggest that retention of inorganic phosphate by muscle despite hypophosphatemia represents a fundamental, vital process to maintain cellular integrity.

Another investigator has examined skeletal muscle inorganic phosphate, ATP and ADP concentrations in dogs with chronic phosphate deficiency (T. J. Fuller, MD, University of Florida, Gainesville, unpublished observation, 1979). Each component fell by approximately 50 percent. The phosphorylation potential became twice normal, indicating that the cell's capacity to produce ATP was reduced. Because the content of ATP is low, such a cell is in a state of peril should there appear a demand for energy production. For example, if inorganic phosphate cannot be maintained in the face of acute hypophosphatemia, ATP levels would decrease further and disintegration might follow.[41] Fuller's findings probably explain why superimposition of severe hypophosphatemia on a cell already injured by chronic phosphate deficiency causes florid rhabdomyolysis[13] and perhaps explain why papillary muscles of phosphate-deficient rats fail to recover after an ischemic interval.[23]

It would seem possible that cells injured by a variety of noxious agents or conditions (such as ethanol, malnutrition, acute starvation, uremia, anoxia or a host of metabolic derangements) could be easily destroyed in the event of severe hypophosphatemia. A preceding injury would only need to compromise those mechanisms responsible for maintaining an optimal concentration of inorganic phosphate in the cell. Thereby, both energy production and the adenylate pool would become inadequate to sustain vital cellular functions.

Treatment of Acute Severe Hypophosphatemia

In any discussion of treatment, the issue of efficacy should be given first consideration. Thus, what evidence exists showing that prevention or treatment of hypophosphatemia is beneficial?

Clinical Evidence

Several older as well as more recent studies provide strong support that correction of phosphate deficiency and hypophosphatemia may be important. Many years ago Friedländer studied cases of diabetes mellitus and found that simultaneous administration of phosphate salts with glucose improved glucose utilization.[49] DeFronzo and Lange[5] recently carried out studies in patients with chronic phosphate deficiency and mild hypophosphatemia that resulted from renal tubular disorders or vitamin D resistant rickets. Each of the patients had impaired glucose utilization. Employing the glucose clamp technique, the study showed that glucose intolerance was not the result of impaired insulin secretion but the consequence of impaired tissue sensitivity to insulin. The effect of phosphate repletion was not examined. Franks

and his associates[50] compared two groups of patients with diabetic ketoacidosis. When phosphate salts were administered in association with conventional therapy, recovery was hastened.

The central nervous system complications of acute severe hypophosphatemia observed during hyperalimentation of wasted patients do not occur if adequate phosphate is provided to prevent hypophosphatemia. Brain dysfunction, electroencephalographic abnormalities and decreased erythrocyte 2,3-DPG content revert to normal if hypophosphatemia is corrected.[18]

Patients with hereditary fructose intolerance show sharp increments in the excretion of inosine and uric acid after challenge with fructose.[46] Administration of phosphate supplements with fructose reduces excretion of both inosine and uric acid. These observations suggest that cytosolic depletion of inorganic phosphate and depletion of the adenylic acid pool are both attenuated in these patients by administration of phosphate.

Administration of calories without adequate phosphate during refeeding therapy led to the rapid development of severe metabolic acidosis in children with protein-calorie malnutrition due to lactase deficiency.[51] However, phosphate supplementation resulted in a sharp increase of titratable acid in the urine and rapid correction of metabolic acidosis.

Finally, Darsee and Nutter[22] and O'Connor and his associates[21] have shown, respectively, improvement in congestive cardiomyopathy and calculated ventricular work associated with profound hypophosphatemia following administration of phosphate salts. In Darsee's patients, recovery occurred without simultaneous administration of digitalis or diuretics.

Experimental Evidence

Abundant experimental evidence indicates that prevention or treatment of hypophosphatemia may be advantageous. Morris and his associates[47] studied the effect of fructose-loading in rats. The decline of ATP, ADP and inorganic phosphate in liver and renal cortical tissue was substantially less if fructose was given with phosphate.

In our own studies the acute florid rhabdomyolysis produced by hyperalimentation of partially starved, phosphate-deficient dogs did not occur if large quantities of inorganic phosphate were added to the hyperalimentation mixture to prevent hypophosphatemia.[13] When hyperalimented without phosphate, the same animals displayed pronounced weakness, tremors, fasciculations and, in many instances, convulsions before death. None of these events occurred when adequate phosphate supplementation was provided.

In experiments involving chronic phosphate-deficient dogs, studies of skeletal muscle showed a rise of sodium chloride content and water, and a decrease in the transmembrane-resting electrical potential difference. Restoration of inorganic phosphate to the diet led to correction of these abnormalities.[12] And in another study, impaired contractile force and decreased left ventricular ejection rates in phosphate-deficient dogs were effectively reversed by phosphate repletion.[20]

Finally, guinea pigs administered graded doses of *Salmonella* organisms regularly became hypophosphatemic as a result of hyperventilation and respiratory alkalosis. The LD_{50} was increased by administration of sufficient phosphate to prevent hypophosphatemia.[26]

The foregoing is considered to be persuasive clinical and experimental evidence that treatment of phosphate deficiency and hypophosphatemia is not only important but effective. However, in those situations where tissue destruction has already occurred, benefit would not be expected. A review has been published offering recommendations for management of phosphate deficiency and hypophosphatemia.[52]

General Management

The general principles of management for phosphate deficiency and hypophosphatemia are similar to those for deficiency of many other ions or minerals. First, if a person can tolerate oral administration of the supplement, it should be administered by this route. Milk is an excellent source of phosphate as well as of potassium and calcium. Its phosphate content is approximately 33 mmoles per quart. In some cases, however, patients with severe phosphate deficiency cannot tolerate lactose or fat. Therefore, if milk cannot be used one might attempt administration of buffered sodium phosphate orally. In the presence of phosphate deficiency and otherwise normal intestinal function, the capacity for phosphate absorption may be enhanced so that the usual expectation of diarrhea with administration of sodium phosphate salts does not occur.

In most instances of severe hypophosphatemia it is necessary to administer phosphate salts intravenously. One should select an intravenous preparation, become acquainted with its contents and,

ideally, administer the compound in a quantity that will not produce hyperphosphatemia. Hypocalcemia and metastatic calcification are distinct hazards of intravenous administration of phosphate salts. Two recent publications studied this problem in children undergoing treatment for diabetic ketoacidosis.[53,54] A special problem may also exist in patients who are simultaneously hypophosphatemic, hypokalemic and hypomagnesemic. Infusion of phosphate (PO_4) salts will lower ionized calcium if the product of calcium and phosphorus exceeds 2.4 to 2.5×10^{-6} moles per liter (58 mg per dl). Herbert and his associates[55] examined the effect of infusing 1.8 mmoles of PO_4 per kg of body weight into normal subjects and observed a fall of serum calcium that averaged 0.18 mmole per liter (-0.7 mg per dl). In one patient with hypoparathyroidism, 1.3 mmoles of PO_4 per kg of body weight reduced serum calcium from 2.1 to 1.8 mmoles per liter (-1.2 mg per dl). If serum calcium is low before administration of PO_4 salts, an appreciable fall of serum calcium would not be anticipated if the solubility product were not exceeded. In healthy subjects, a fall of calcium produced by PO_4 infusion would be in part corrected by release of parathyroid hormone. However, if a patient also has hypomagnesemia, release of parathyroid hormone would be suppressed[56] and, in turn, hypocalcemia could conceivably become more severe and prolonged. Alkalosis could potentiate the tendency for formation of calcium phosphate and thereby enhance hypocalcemia.

Patients being treated for diabetic ketoacidosis, alcoholic patients in withdrawal and patients with steatorrhea often have hypophosphatemia, hypomagnesemia, hypocalcemia and hypokalemia. In such patients, electrolyte replacement solutions should include phosphate, magnesium and potassium. However, lest the conclusion be made that it might be best to avoid phosphate altogether, the natural course of diabetic ketoacidosis should be considered.

Without phosphate treatment, Martin and his co-workers[57] found that 73 percent of adults treated for diabetic ketoacidosis became hypocalcemic and 55 percent became hypomagnesemic. In Zipf's study,[53] nine children with diabetic ketoacidosis were given phosphate salts, and five became hypocalcemic. In the latter study, hypomagnesemia was present in each patient, but fell below 1 mEq per liter in only one. The dosage of phosphate in the children who had the most severe hypocalcemia was greater than 11 mmoles per kg of body weight per 24 hours. Serum phosphorus was also high. Winter and his co-workers[54] described a 9-year-old child with diabetic ketoacidosis in whom hypocalcemia and hypomagnesemia developed after administration of more than 5 mmoles of phosphate per kg of body weight in 29 hours. Based upon such data, hypocalcemia occurs in most patients during treatment of diabetic ketoacidosis whether or not phosphate is given. In addition, if large doses of phosphate are given, hypocalcemia can be seriously aggravated.

In treating adult patients with hypophosphatemia, a rule of thumb that continues to be successful in our patients is administration of approximately 20 mmoles of sodium phosphate intravenously each eight hours. Using this formula, the total daily dose is less than 1 mmole per kg of body weight. This amount has generally been adequate to maintain serum phosphorus levels of at least 1.5 mg per dl. This concentration appears to prevent most of the severe consequences of hypophosphatemia and at the same time should be sufficiently low to prevent hyperphosphatemia and precipitation of calcium phosphate in tissues.

If confronted with the complex electrolyte derangements as described in cases of alcoholic withdrawal, it is practical to administer phosphate, magnesium and potassium in the same solution. For example, we have used solutions composed of 1 liter of 5 percent glucose in 0.45 percent saline, to which have been added 20 mmoles of potassium phosphate, 20 mEq of potassium chloride and 20 ml of 50 percent magnesium sulfate (16 mEq of magnesium). This quantity is infused over eight hours. We have infused this mixture three times a day for several days in many patients with successful results. The three electrolytes are compatible in solution. Used in such quantities, we have not encountered severe hypocalcemia. Obviously, intravenously given phosphate should not be administered in the presence hyperphosphatemia.

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